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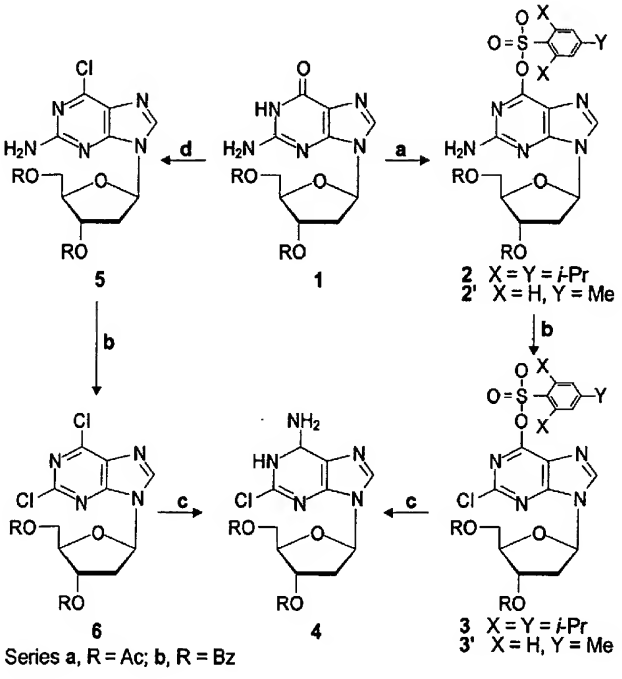
(54) Title: METHOD FOR THE PREPARATION OF 2-HALO-2'-DEOXYADENOSINE COMPOUNDS FROM 2'-DEOXYGUANOSINE



[a] (a) TiPBS-Cl/Et_3N/DMAP/CH_2Cl_2. (b) AcCl/BTEA-NO_2/CH_2Cl_2/–5 to 0 °C. (c) NH_3/MeOH/CH_2Cl_2/Δ. (d) $POCl_3$/BTEA-Cl/*N,N*-dimethylaniline/MeCN/Δ.

(57) Abstract: The present invention is a method for preparing 2-halo-6-aminopurines, and more specifically for preparing the clinical agent cladribine (2-chloro-2'-deoxyadenosine, C1dAdo, 4), a drug of choice against hairy-cell leukemia and other neoplasms, from 2-amino-6-oxopurines, which are readily obtained from the naturally occurring compound 2'deoxyguanosine. According to the methods of the present invention, the 6-oxo group of a protected 2'-deoxyguanosine (1) is converted to a 6-(substituted oxy) leaving group, or alternatively to a 6-chloro leaving group, the 2-amino group is replaced with a 2-chloro group, the 6-(substituted oxy) leaving group, or alternatively the 6-chloro leaving group, is replaced with a 6-amino group or, alternatively, a 2,6-dichloro substituted compound is selectively replaced group, and the protecting groups are removed.

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TITLE OF THE INVENTION

Method for the Preparation of 2-Halo-2'-Deoxyadenosine Compounds from 2'-Deoxyguanosine.

FIELD OF THE INVENTION

The present invention is directed to processes for preparing 2-halo-6-aminopurines, and more particularly to a process for preparing 2-chloro-2'-deoxyadenosine.

BACKGROUND OF THE INVENTION

The lymphoselective toxicity of 2-chloro-2'-deoxyadenosine (CldAdo, cladribine) and its potential as a chemotherapeutic agent against lymphoid neoplasms were reported by Carson et al.[1] This potent, deaminase-resistent analogue of 2'-deoxyadenosine (dAdo) is currently the drug of choice for hairy-cell leukemia.[2,3] It also has significant activity against chronic lymphocytic leukemia,[4,5] indolent non-Hodgkin's lymphoma,[6] and Waldenström's macroglobulinemia.[7] Investigations with cladribine treatment of multiple sclerosis,[8] systemic lupus erythematosis-associated glomerulonephritis,[9] and other rheumatoid and immune disorders are in progress. Cladribine is a nucleoside prodrug, which is phosphorylated by deoxycytidine kinase to CldAMP, and then sequentially to CldADP and the active CldATP.[1a,10a] Cladribine also is a good substrate for mitochondrial 2'-deoxyguanosine (dGuo) kinase,[10] and induction of programmed cell death by direct effects on mitochondria has been implicated in its potent activity against indolent lymphoid malignancies (via apoptosis) as well as in proliferating cells.[11,12]

Various methodologies have been published for the production of Cladribine. Venner reported Fischer-Helferich syntheses of naturally occurring 2'-deoxynucleosides in 1960,[13] and employed 2-chloro-2'-deoxyadenosine as an intermediate for 2'-deoxy(guanosine and inosine). Ikehara and Tada also synthesized dAdo with CldAdo as an intermediate [obtained by desulfurization of 8,2'-anhydro-9-(β-D-arabinofuranosyl)-2-chloro-8-thioadenine].[14]

Syntheses of CldAdo as a target compound have exploited the greater reactivity of leaving groups at C6 relative to those at C2 of the purine ring in S_NAr displacement reactions. Robins and Robins[15] employed fusion coupling of 2,6-dichloropurine with 1,3,5-tri-*O*-acetyl-2-deoxy-α-D-ribofuranose. The 9-(3,5-di-*O*-acetyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-2,6-dichloropurine anomer was obtained by fractional crystallization. Selective ammonolysis at C6 and accompanying deprotection gave 6-amino-2-chloro-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine. The pharmacologically active β-anomer (cladribine) was prepared by an analogous coupling, chromatographic separation of anomers, and ammonolysis.[16]

Stereoselective glycosylation of sodium salts of halopurines and analogues with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride gave β-nucleoside anomers via predominant Walden inversion,[17,18] and ammonolysis/deprotection gave CldAdo.[19] Although the sodium salt glycosylation usually gave good anomeric stereoselectivity, minor quantities of α anomers and >10% of N7 regioisomers were usually formed.[20,21] This requires separations and results in diminished yields of the desired N9 product. Carson et al.[1] had reported an enzymatic transfer of the 2-deoxy sugar from thymidine to 2-chloroadenine (ClAde). Holy and coworkers noted that cells of a strain of *Escherichia coli* performed glycosyl transfer from 2'-deoxyuridine to 2-chloro-6-[(dimethylaminomethylene)amino]purine to give a derivative of CldAdo.[22] Very recently Barai, Mikhailopulo, and coworkers[23] described an *E. coli*-mediated glycosyl transfer synthesis of 2,6-diamino-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)purine,[24] and its enzymatic deamination to 3'-deoxyguanosine.[24] They reported glycosyl transfer from 2'-deoxyguanosine to ClAde, and claimed a yield of 81% of CldAdo (based on ClAde).[23] However, a 3:1 ratio of dGuo/ClAde was employed, so the yield of CldAdo was <27% based on dGuo.

Sampath et al. have recently shown (U.S. Patent No. 6,596,858 B2) a method for making 2-chloro-2'-deoxyadenosine compounds, using 2-amino-2'-deoxyadenosine as a starting compound, but beginning with an initial diazotization/chloro-dediazoniation reaction on the unprotected nucleoside to replace the 2-amino group with a 6-chloro group. This method, however, creates various impurities, which requires extensive purification procedures, and results in an overall yield of only 27%.

Accordingly, there is a significant need to produce CldAdo using methods that result in a higher yield, are more cost effective, and result in a more purified form.

SUMMARY OF THE INVENTION

The present invention is a method for producing 2-chloro-2'-deoxyadenosine (CldAdo) comprising the steps of: (a) converting the 6-oxo group of a compound having the formula (1) wherein R is a protecting group, into a 6-leaving group having sufficient reactivity for an S_NAr displacement reaction; (b) replacing the 2-amino group with a 2-chloro group in a diazotization/chloro-dediazoniation reaction; (c) replacing the 6-leaving group with a 6-amino group; and (d) removing the R protecting groups, to produce 2-chloro-2'-deoxyadenosine.

DESCRIPTION OF THE FIGURES

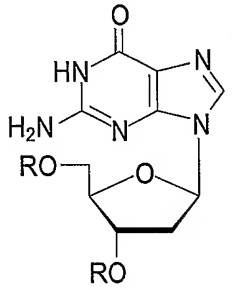
Figure 1 shows the chemical synthesis of 2-chloro-2'-deoxyadenosine from protected forms of naturally occurring 2'-deoxyguanosine.

Figure 2 shows the diazotization/halo-dediazoniation conversion reaction from a 2-aminopurine nucleoside to a 2-halopurine nucleoside.

DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

In accordance with the present invention, synthesis of regio- and stereochemically pure 2-chloro-2'-deoxyadenosine (Cladrabine, or CldAdo), which avoids separation of mixtures with fusion and sodium salt glycosylation procedures, is accomplished by

transformation of the naturally occurring nucleoside 2'-deoxyguanosine (dGuo) as the starting compound.[24] Methods for producing CldAdo from 2'-deoxyguanosine (dGuo) according to the present invention begin with protected forms of dGuo including, but not restricted to, acyl, silyl, amide, and other derivatives useful in the field of nucleoside/nucleotide/nucleic acid chemistry and protection strategies. Methods for obtaining protected forms of dGuo are well-known in the art.[25,26,27,28,29,30] The preferred starting products for efficient synthesis of CldAdo are defined by the following chemical structure:



where R is any suitable protecting group, and preferably R is Ac or Bz.

In order to obtain the desired CldAdo compounds, protected dGuo derivatives are treated with combinations of chemicals that effect functionalization at the C6 position to give groups that can be replaced, followed by transformation of the 2-amino function to a 2-chloro group, followed by replacement of the 6-functional group to give a 6-amino group (or a 6-substituent that can be converted into a 6-amino group, followed by conversion to the 6-amino group), and concomitant or subsequent deprotection of the resulting 6-amino-2-chloropurine derivative to give CldAdo. For example, from dGuo, CldAdo (**4**) (Figure 1) is synthesized by converting the 6-oxo function into appropriate 6-(substituted oxy) leaving groups that can be replaced without protection of the 2-amino moiety, transformation of the

6-chloro derivatives **5a** (90%) and **5b** (85%) were obtained in high yields under carefully controlled conditions.

Following the step of converting the 6-oxo group to a 6-(substituted oxy) leaving group, the 2-amino group is replaced with a 2-chloro group by a diazotization/halo-dediazoniation reaction. Improved methods are disclosed for replacement of an amino group on purine nucleoside derivatives with chlorine, bromine, or iodine under non-aqueous conditions by diazotization/halo-dediazoniation methods.[27] These mild diazotization/halo-dediazoniation methods are applicable at C6 of dAdo derivatives as well as at C2 of 2-amino-6-chloropurine nucleosides. In accordance with the present invention, CldAdo is produced from dGuo by treatment of protected forms of dGuo that contain a respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl group with reagents that effect diazotization/chloro-dediazoniation at C2 to give a 2-chloro group. CldAdo is also produced by treating protected 2-amino-6-chloropurine derivatives with reagents that effect diazotization/chloro-dediazoniation at C2 to give respective 2,6-dichloropurine derivatives.

Reagents that effect diazotization/chloro-dediazoniation at C2 to give a 2-chloro group include a halide source (such as metal chlorides, metal chloride salts, acyl chlorides, sulfonyl chlorides, and silyl chlorides, alkyl and aryl substituted ammonium chloride salts, including but not limited to tetraalkyl and aryl ammonium chloride salts) and a nitrite source (such as metal nitrites, metal nitrite salts, organic nitrites, such as tert-butyl nitrite, pentyl nitrite, and isoamyl nitrite, and complex quaternary ammonium nitrites, such as benzyltriethylammonium nitrite).

In preferred embodiments of the present invention, CldAdo is synthesized by employing acetyl chloride and benzyltriethylammonium nitrite (BTEA-NO_2)-mediated diazotization/chloro-dediazoniation of 6-*O*-(2,4,6-triisopropylbenzenesulfonyl) (TiPBS) or 6-chloro derivatives that are readily obtained from dGuo. Non-aqueous diazotization/chloro-

dediazoniation (acetyl chloride/benzyltriethylammonium nitrite) of **2**, **2'b**, or **5** gave the 2-chloropurine derivatives **3**, **3'b**, or **6**, respectively. This new procedure for non-aqueous diazotization/chloro-dediazoniation[27] (AcCl/BTEA-NO_2/CH_2Cl_2/–5 to 0 °C) worked well for replacement of the 2-amino group of **2**, **2'b**, and **5** with chlorine to give **3a** (89%), **3b** (90%), **3'b** (87%), **6a** (95%), and **6b** (91%).

Efficient diazotization/chloro-dediazoniation of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-amino-6-chloropurine[26,33] (**7**) (Figure 2) was effected with TMS-Cl (9 equivalents) and benzyltriethylammonium nitrite (BETA-NO_2) (3 equivalents) in CH_2Cl_2 at ambient temperature. The process was rapid (<30 min), and the desired 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloropurine[27,37] (**8**) (83%, without chromatography) was obtained as a white crystalline solid. Comparable yields were obtained at 0° C. TMS-Cl (3.5 equivalents) and BTEA-NO_2 (1.5 equivalents) with powdered $NaNO_2$ (5 equivalents) gave **8** (86%) within 1 hr. By contrast, an alternative method for non-aqueous diazotization/chloro-dediazoniation of **7** employed Cl_2/TBN/CuCl in a strongly exothermic reaction, and removal of colloidal material by filtration was required prior to crystallization of **7**.[35]

Compound **7** underwent efficient diazotization/bromo-dediazoniation with TMS-Br and tert-butyl nitrite (TBN). Competing redox interactions between nitrite anion and TMS-Br precluded the use of $NaNO_2$. The 2-bromo-6-chloropurine nuclcoside **3**[27,37] (85%, without chromatography) was obtained as a crystalline solid with TMS-Br (9 equivalents)/TBN (20 equivalents)/CH_2Br_2/ambient temperature within 1 h.

NOCl/CH_2Cl_2 or NOBr/CH_2Br_2 is presumed to be generated from (Me_3SiX or AcCl) and (TBN or BTEA-NO_2). These procedures provide efficient diazotization/halo-dediazoniation of protected (2 or 6)-aminopurine nucleosides as well as the acid-sensitive 2'-deoxynucleosides. The reactions are cost-effective and proceed at or below ambient temperature with convenient reagents and standard laboratory equipment and conditions.

Following replacement of the 2-amino group with a 2-chloro group, the protected forms of dGuo that contain a respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl or phosphoryl group and a 2-chloro group is reacted with chemicals that cause replacement of the 6-*O*-(alkyl, cycloalkyl, or aryl) sulfonyl or phorphoryl group to give a 6-amino group (or a substituent that can be converted into a 6-amino group, resulting in overall conversion of the substituent into a 6-amino group) of a resulting 6-amino-2-chloropurine derivative. In preferred embodiments, the 6-leaving group is replaced with a 6-amino group by reacting the product of step (b) with a nitrogen source capable of being converted to an amino group in a solvent compatible with the nitrogen source to replace the 6-leaving group with a 6-amino group by selective ammonolysis of the 6-leaving group. The nitrogen source is selected from the group consisting of ammonia, azides, hydrazines, benzylic amines, or compatible ammonium salts. The solvent may be any solvent that is compatible with the nitrogen source, such as methanol, ethanol, higher alcohols, or aprotic solvents, such as 1,2-dimethoxyethane, tetrahydrofuran, or DMF.

In other preferred embodiments, the respective 6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl leaving group is reacted with ammonia in a compatible aprotic solvent to give a 6-amino-2-chloropurine derivative, followed by deprotection (if necessary) to give CldAdo. In a more preferred embodiment, a 9-(3,5-di-*O*-acyl-β-D-*erythro*-pentofuranosyl-6-*O*-(alkyl, cycloalkyl, or aryl)sulfonyl-2-chloropurine is treated with ammonia in methanol or other compatible solvent to give CldAdo.

Further, protected derivatives of 2,6-dichloropurine are treated with reagents that cause selective replacement of the 6-chloro group to give a 6-amino group (or a substituent that can be converted into a 6-amino group, followed by conversion of the substituent into a 6-amino group) of a resulting 6-amino-2-chloropurine derivative. In a more preferred

embodiment, 9-(3,5-di-*O*-acyl-β-D-*erythro*-pentofuranosyl)-2,6-dichloropurine is treated with ammonia in methanol or other compatible solvent to give CldAdo.

Selective ammonolysis at C6 (arylsulfonate with **3** or chloride with **6**) and accompanying deprotection of the sugar moiety gave CldAdo (**4**) (64–75% overall from **1**). Specifically, displacements of the hindered arylsulfonate (from **3**) or chloride (from **6**) at C6 with accompanying cleavage of the sugar esters were effected at 80 °C with NH_3/MeOH/CH_2Cl_2. Cladribine (**4**) was obtained in high yields from **3a** (81%), **3b** (83%), **6a** (87%), and **6b** (94%), but only in moderate yield from the 6-*O*-tosyl derivative **3'b** (43%).

The R protecting groups are removed by deacylation using a basic reagent well known in the art in a solvent compatible with the basic reagent, to remove the R protecting groups and produce 2-chloro-2'-deoxyadenosine. The basic reagent is selected from the group consisting of ammonia, metal alkoxides, metal hydroxides, and metal carbonates. The solvent may be any solvent that is compatible with the basic reagent, such as methanol, ethanol, 1,2-dimethoxyethane/H_2O, or tetrahydrofuran/H_2O.

It is to be noted that removal of the R protecting groups may occur concomitantly with or subsequent to the replacement of the 6-(substituted oxy) leaving group with a 6-amino group by ammonolysis. Both steps of replacement of the 6-(substituted oxy) leaving group with a 6-amino group and removal of the R protecting groups is accomplished by use of a nitrogen source in a solvent compatible with the nitrogen source. Where the nitrogen source is ammonia in a protic solvent, such as methanol or ethanol, both steps proceed simultaneously. However, where the nitrogen source is anhydrous ammonia in a dry solvent, such as 1,2-dimethoxyethane, or tetrahydrofuran, only the step of replacement of the 6-(substituted oxy) leaving group with a 6-amino group proceeds. In this case, it is necessary and sometimes desirable to remove the R protecting groups in a separate step.

(nucleoside/NH_3/MeOH/Δ) for **3a** → **4**. Analogous reactions with equivalent molar proportions of other nucleosides gave the indicated products and quantities.

Example 1

Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-amino-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (2a). Method 1. Et_3N (1.25 mL, 910 mg, 9.0 mmol) was added to a stirred solution of **1a** (1.67 g, 4.8 mmol), TiPBS-Cl (2.73 g, 9.0 mmol), and DMAP (72 mg, 0.6 mmol) in dried $CHCl_3$ (70 mL) under N_2. Stirring was continued for 24 h, and volatiles were evaporated. The orange residue was chromotographed (CH_2Cl_2/MeOH) give **2a**[32] (2.67 g, 91%) as a slightly yellow foam with UV max 238, 291 nm, min 264 nm; ^{1}H NMR (500 MHz) δ 1.26–1.32 (m, 18H), 2.08 (s, 3H), 2.14 (s, 3H), 2.54 (ddd, J = 4.7, 9.0, 14.0 Hz, 1H), 2.91–2.99 (m, 2H), 4.22–4.37 (m, 3H), 4.43–4.47 (m, 2H), 4.97 (br s, 2H), 5.41–5.42 ("d", 1H), 6.26–6.29 (m, 1H), 7.21 (s, 2H), 7.84 (s, 1H); LRMS *m/z* 618 (MH^+ [$C_{29}H_{40}N_5O_8S$] = 618); HRMS *m/z* 640.2413 (MNa^+ [$C_{29}H_{39}N_5O_8SNa$] = 640.2417).

Example 2

Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-*O*-(2,4,6-triisopropylbenzenesulfonyl) purine (2b). Treatment of **1b** (950 mg, 2.0 mmol) by method 1 gave **2b** (1.27 g, 86%) as a white solid foam with UV max 289 nm, min 264 nm; ^{1}H NMR δ 1.29–1.32 (m, 18H), 2.76 (ddd, J = 2.1, 6.0, 14.3 Hz, 1H), 2.96 ("quint", J = 6.8 Hz, 1H), 3.15–3.25 (m, 1H), 4.34 ("quint", J = 6.8 Hz, 2H), 4.65–4.74 (m, 2H), 4.85–4.90 (m, 1 H), 5.00 (br s, 2H), 5.84–5.86 ("d", 1H), 6.38–6.43 (m, 1H), 7.30 (s, 2H), 7.44–7.55 (m, 4H), 7.58–7.69 (m, 2H), 7.85 (s, 1H), 8.04 (d, J = 7.1 Hz, 2H), 8.11 (d, J = 7.1 Hz, 2H); LRMS *m/z* 742 (MH^+ [$C_{39}H_{44}N_5O_8S$] = 742), 764 (MNa^+ [$C_{39}H_{43}N_5O_8SNa$] = 764); HRMS *m/z* 764.2730 (MNa^+ [$C_{39}H_{43}N_5O_8SNa$] = 764.2730).

Example 3

Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-*O*-(4-methylbenzenesulfonyl)purine (2'b). Et_3N (700 μL, 506 mg, 5.0 mmol) was added to a stirred solution of **1b** (1.43 g, 3.0 mmol), TsCl (858 mg, 4.5 mmol), and DMAP (36 mg, 0.3 mmol) in dried $CHCl_3$ (45 mL) under N_2. Stirring was continued for 15 h, and volatiles were evaporated. The slightly yellow residue was chromotographed (CH_2Cl_2/MeOH) to give **2'b** (1.68 g, 89%) as a white solid foam with UV max 300 nm; ^1H NMR (DMSO-d_6) δ 2.43 (s, 3H), 2.73 (ddd, J = 2.1, 8.4, 14.4 Hz, 1H), 3.17–3.27 ("quint", J = 7.2 Hz, 1H), 4.52–4.65 (m, 3H), 5.76–5.78 ("d", 1H), 6.37–6.41 (m, 1H), 6.95 (br s, 2H), 7.47–7.73 (m, 8H), 7.95 (d, J = 7.8 Hz, 2H), 8.03–8.11 (m, 4H), 8.30 (s, 1H); LRMS *m/z* 630 (MH^+ [$C_{31}H_{28}N_5O_8S$] = 630), *m/z* 652 (MNa^+ [$C_{31}H_{27}N_5O_8SNa$] = 652); HRMS *m/z* 652.1467 (MNa^+ [$C_{31}H_{27}N_5O_8SNa$] = 652.1478).

Example 4

Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3a). Method 2. A solution of AcCl (200 μL, 220 mg, 2.8 mmol) in dried CH_2Cl_2 (12 mL) under N_2 was chilled in a NaCl/ice/H_2O bath (–5 to 0 °C) for 15 min. BTEA-NO_2 (520 mg, 2.2 mmol) was dissolved in dried CH_2Cl_2 (8 mL) and this solution was immediately added dropwise to the cold, stirred solution of AcCl/CH_2Cl_2. A solution of **2a** (288 mg, 0.5 mmol) in dried CH_2Cl_2 (5 mL) was then added dropwise to the cold solution, and stirring was continued for 5 min (TLC, CH_2Cl_2/MeOH, 95:5, showed complete conversion of **2a** into a single product). The reaction mixture was added dropwise at a rapid rate to a cold (ice/H_2O bath), vigorously stirred mixture of saturated $NaHCO_3$/H_2O (100 mL)//CH_2Cl_2 (100 mL). The layers were separated, and the organic phase was washed with cold (0 °C) H_2O (2 X 100 mL) and dried ($MgSO_4$) for 1 h. Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH) to give **3a**

(267 mg, 89%) as a white solid foam with UV max 240, 266 nm, min 255 nm; 'H NMR (500 MHz) δ 1.24–1.31 (m, 18H), 2.08 (s, 3H), 2.13 (s, 3H), 2.67 (ddd, J = 2.5, 7.0, 15.5 Hz, 1H), 2.76–2.81 (m, 1H), 2.90–2.96 ("quint", J = 7.0 Hz,1H), 4.28–4.33 ("quint", J = 7.0 Hz, 2H), 4.35–4.39 (m, 3H), 5.38–5.39 ("d", 1H), 6.42–6.45 (m, 1H), 7.22 (s, 2H), 8.23 (s, 1H); LRMS *m/z* 637 (MH^+ [$C_{29}H_{38}ClN_4O_8S$] = 637); HRMS *m/z* 659.1902 (MNa^+ [$C_{29}H_{37}ClN_4O_8SNa$] = 659.1918).

Example 5

Preparation of 9-(3,5-Di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3b). Treatment **2b** (1.20 g, 1.6 mmol) by method 2 gave **3b** (1.10 g, 90%) as a yellow solid foam with UV max 230, 266 nm, min 255 nm; ^1H NMR δ 1.22–1.34 (m, 18H), 2.92–3.00 (m, 3H), 4.30–4.34 (m, 2H), 4.68–4.77 (m, 3H), 5.80–5.82 ("d", 1H), 6.54–6.57 (m, 1H), 7.42–7.64 (m, 8H), 8.00 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H); HRMS *m/z* 783.2224 (MNa^+ [$C_{39}H_{41}ClN_4O_8SNa$] = 783.2231).

Example 6

Preparation of 9-(3,5-Di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(4-methylbenzenesulfonyl)purine (3'b). Treatment of **2'b** (1.45 g, 2.3 mmol) by method 2 gave **3'b** (1.30 g, 87%) as a slightly yellow foam with UV max 267 nm, min 255 nm; ^1H NMR (DMSO-d_6) δ 2.45 (s, 3H), 2.86 (ddd, J = 3.4, 6.2, 14.0 Hz, 1H), 3.21–3.30 ("quint", J = 7.0 Hz, 1H), 4.55–4.67 (m, 3H), 5.82–5.84 (m, 1H), 6.56–6.61 (m, 1H), 7.42–7.72 (m, 8H), 7.88 (d, J = 7.8 Hz, 2H), 8.04–8.07 (m, 4H), 8.88 (s, 1H); HRMS *m/z* 671.0983 (MNa^+ [$C_{31}H_{25}ClN_4O_8SNa$] = 671.0979.

Example 7

Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2-amino-6-chloropurine (5a). Method 3. A mixture of **1a** (540 mg,, 1.54 mmol), BTEA-Cl (710 mg,

3.1 mmol), *N,N*-dimethylaniline (215 μL, 206 mg, 1.7 mmol), and $POCl_3$ (720 μL, 1.2 g, 7.7 mmol) in MeCN (6 mL) was stirred in a preheated oil bath (85 °C) for 10 min. Volatiles were flash evaporated immediately (in vacuo), and the yellow foam was dissolved ($CHCl_3$, 15 mL) and stirred vigorously with crushed ice for 15 min. The layers were separated, and the aqueous phase was extracted ($CHCl_3$, 3 X 5 mL). Crushed ice was frequently added to the combined organic phase, which was washed [(ice-H_2O (3 X 5 mL), 5% $NaHCO_3/H_2O$ (to pH ~7)] and dried ($MgSO_4$). Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH) to give **5a**[36,38] (517 mg, 90%) as a white solid foam with UV max 248, 310 nm, min 268 nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (s, 3H), 2.08 (s, 3H), 2.49–2.52 (m, 1H), 3.04–3.06 (m, 1H), 4.20–4.29 (m, 3H), 5.32–5.34 ("d", 1H), 6.23–6.26 (m, 1H); 7.03 (br s, 2H), 8.35 (s, 1H); ^{1}H NMR δ 2.03 (s, 3H), 2.08 (s, 3H), 2.51 (ddd, J = 2.7, 5.9, 14.2 Hz, 1H), 2.85–2.94 ("quint", J = 7.1 Hz, 1H), 4.28–4.42 (m, 3H), 5.35–5.37 (m, 1H), 6.21–6.26 (m, 1H), 7.89 (s, 1H); HRMS (EI) *m/z* 369.0844 (M^+ [$C_{14}H_{16}ClN_5O_5$] = 369.0840).

Example 8

Preparation of 2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-chloropurine (5b). Treatment of **1b** (2.38 g, 5 mmol) by method 3 gave **5b** (2.10 g, 85%) as a slightly yellow solid foam with UV max 310 nm; ^{1}H NMR (DMSO-d_6) δ 2.69–2.78 ("ddd", 1H), 3.20–3.24 ("quint", J = 7.2 Hz, 1H), 4.56–4.67 (m, 3H), 5.77–5.79 ("d", 1H), 6.39–6.44 (m, 1H), 7.02 (br s, 2H), 7.48–7.71 (m, 6H), 7.96 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 8.37 (s, 1H); LRMS *m/z* 494 (MH^+ [$C_{24}H_{21}ClN_5O_5$] = 494); HRMS *m/z* 516.1042 (MNa^+ [$C_{24}H_{20}ClN_5O_5Na$] = 516.1051).

Example 9

Preparation of 9-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-2,6-dichloropurine (6a). Treatment of **5a** (265 mg, 0.7 mmol) by method 2 gave **6a**[39] (266 mg,

Method C. A solution of AcCl/CH_2Cl_2 (1 M, 2.5mL, 2.5 mmol) was added to dried CH_2Cl_2 (10 mL) under N_2, and the solution was cooled for 15 min. BTEA-NO_2 (535.5 mg, 2.25 mmol) in CH_2Cl_2 (5 mL) was then added dropwise (1 drop/2 sec) to the cold, stirred solution of AcCl/CH_2Cl_2. A cold solution of **7** (214 mg., 0.5 mmol) in dried CH_2Cl_2 (5 mL) was then added dropwise to the cooled, stirred AcCl/BETA-NO_2Cl_2 solution (TLC, hexanes/EtOAc, 3:7). Immediate workup and recrystallization (as in method B) gave **8** (187 mg, 84%) as pale-yellow crystals.

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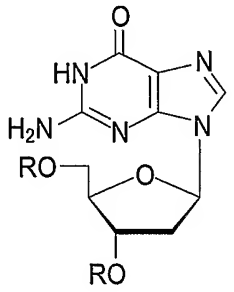
CLAIMS

We claim:

1. A method for producing 2-chloro-2'-deoxyadenosine comprising the steps of:

(a) converting the 6-oxo group of a compound having the formula



wherein R is a protecting group, into a 6-(substituted oxy) group having sufficient reactivity in an S_NAr displacement reaction;

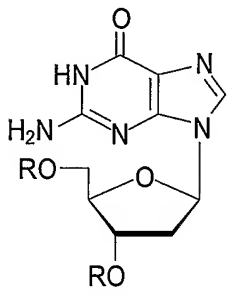
(b) replacing the 2-amino group with a 2-chloro group by a diazotization/chloro-dediazoniation reaction;

(c) replacing the 6-(substituted oxy) leaving group with a 6-amino group; and

(d) removing the R protecting groups, to produce 2-chloro-2'-deoxyadenosine.

5. A method for producing 2-chloro-2'-deoxyadenosine comprising the steps of:

(a) converting the 6-oxo group of a compound having the formula



wherein R is a protecting group selected from the group consisting of acetyl, benzoyl, into a 6-leaving group having greater reactivity than that of the 2-chloro group in an S_NAr displacement reaction;

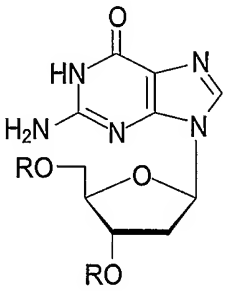
(b) replacing the 2-amino group with a 2-chloro group by diazotization/chloro-dediazoniation of the 2-amino group;

(c) replacing the 6-leaving group with a 6-amino group by selective ammonolysis of the 6-leaving group; and

(d) removing the R protecting groups by deacylation, to produce 2-chloro-2'-deoxyadenosine.

6. A method for producing 2-chloro-2'-deoxyadenosine comprising the steps of:

(a) reacting the 6-oxo group of a compound having the formula



wherein R is a protecting group selected from the group consisting of acyl and silyl, with an (alkyl or any substituted alky or cycloalkyl) sulfonyl or phosphoryl reagent or (aryl or any substituted aryl) sulfonyl or phosphoryl reagent to convert the 6-oxo group to a 6-*O*-(alkyl, cycloalkyl, or aryl) sulfonyl or phosphoryl group;

(b) reacting the product of step (a) with a halide and an organic nitrite in a solvent compatible with the halide to replace the 2-amino group with a 2-chloro group by diazotization/chloro-dediazoniation of the 2-amino group;

(c) reacting the product of step (b) with ammonia in a solvent or with a nitrogen source capable of being converted to an amino group in a solvent compatible with the nitrogen source to replace the 6-leaving group with a 6-amino group by selective ammonolysis of the 6-leaving group; and

(d) reacting the product of step (c) with a basic reagent in a compatible solvent to remove the R protecting groups by deacylation, to produce 2-chloro-2'-deoxyadenosine.

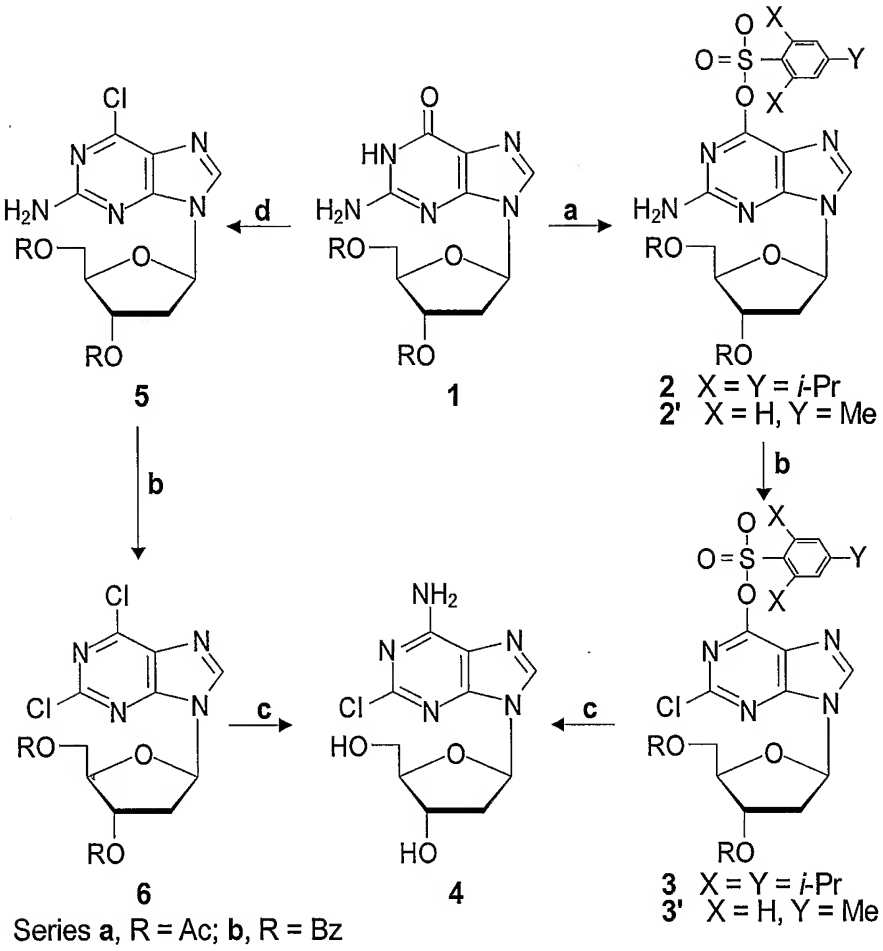


Figure 1

[a] (a) TiPBS-Cl/Et_3N/DMAP/CH_2Cl_2. (b) AcCl/BTEA-NO_2/CH_2Cl_2/–5 to 0 °C. (c) NH_3/MeOH/CH_2Cl_2/Δ. (d) $POCl_3$/BTEA-Cl/*N,N*-dimethylaniline/MeCN/Δ.

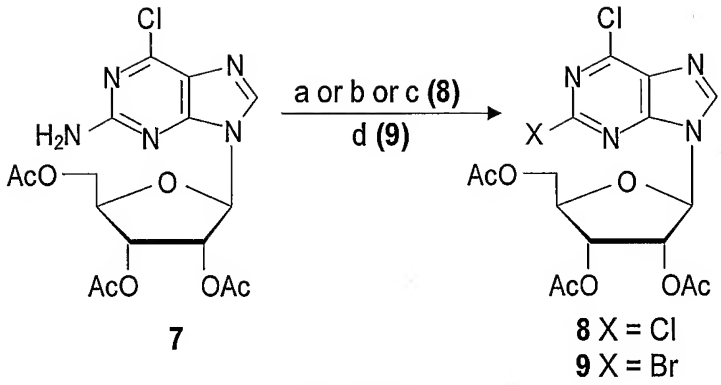


Figure 2

(a) TMS-Cl/BTEA-NO_2/CH_2Cl_2 (83%); (b) TMS-Cl/BTEA-NO_2/$NaNO_2$/CH_2Cl_2 (86%); (c) AcCl/BTEA-NO_2/CH_2Cl_2/0-5 C° (84%); (d) TMS-Br/TBN/CH_2Br_2 (85%)